Efficacy of Mupirocin in Methicillin-Resistant *Staphylococcus aureus* Burn Wound Infection

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Methicillin-resistant *Staphylococcus aureus* strains (MRSA) have become increasingly prevalent as nosocomial pathogens, especially in burn wounds. MRSA constituted 38% of all *S. aureus* isolates in our 25-bed burns unit despite the utilization of a combination of 1% silver sulfadiazine and 0.2% chlorhexidine as topical therapy. Mupirocin, a new antibiotic, has proved in vitro and in vivo to be highly effective in the treatment of MRSA infections. A prospective clinical trial with mupirocin ointment in MRSA burn wound infection was undertaken. Forty-five children with 59 discrete burn wounds and from whom MRSA were isolated were treated with 2% mupirocin ointment under occlusive dressings, applied twice daily for 5 days. The average burned area treated was 8% (range, 2 to 20%) of the total body surface area. The burn wounds were assessed clinically and bacteriologically daily. Mupirocin eliminated MRSA in all 59 wounds treated, with the maximum therapeutic response seen within 4 days. In three wounds, gram-negative organisms persisted after 5 days of topical therapy. Treatment was well tolerated by all children. We recommend that mupirocin in its present polyethylene glycol base should be used only on a selective basis, when current prophylactic topical therapy has failed to control MRSA infection in burns of less than 20% of the total body surface area, and that it should be applied only for a limited period of 5 days. The safety and the efficacy of mupirocin in burns exceeding 20% of the total body surface area need to be established.

Methicillin-resistant *Staphylococcus aureus* strains (MRSA) have since 1961 become increasingly prevalent as pathogenic and invasive organisms (1, 2, 4, 9, 22–24). These highly resistant strains are often found in burn units despite the reported significant reduction in *S. aureus* burn wound infection by using a combination of 1% silver sulfadiazine and 0.2% chlorhexidine digluconate as topical therapy (11, 20). MRSA may cause significant and even lethal infections, with an associated mortality of 20 to 40% among those clinically infected (12, 14, 26, 30).

An encouraging development in the control of MRSA has been the introduction of mupirocin, a new nonsystemic topical antibiotic with excellent in vitro and in vivo activity against clinical isolates of *S. aureus*, including antibiotic-resistant strains (7, 8, 33, 36, 39).

Mupirocin is produced by submerged fermentation of *Pseudomonas fluorescens* NCIB 10586 (15, 19). It contains the 9-hydroxy-nonanoic acid moiety and acts by inhibition of bacterial protein synthesis by specifically and reversibly binding to bacterial isoleucyl tRNA synthetase, thereby preventing isoleucine incorporation into growing protein chains. Its action thus differs from that of other commonly used antibiotics.

Because of the high prevalence of MRSA in our 25-bed burns unit (approximately 38% of all *S. aureus* isolates) and the failure of current topical therapeutic agents to eradicate MRSA, a prospective clinical trial with 2% mupirocin ointment in MRSA burn wound infection was undertaken.

MATERIALS AND METHODS

Forty-five children (age range, 8 months to 12 years; mean, 38 months) were included in the study. The basis for selection was an infected burn wound not responding to topical therapy and from which an MRSA was cultured. No

patient who had impaired renal function, was clinically unstable during the postinjury phase, or had burn wounds exceeding 20% of the total body surface area was considered for mupirocin therapy.

Thermal injuries were caused by hot liquids in 28 of these patients, by fire in 14, and by hot objects in 2. One child sustained a caustic burn to the forearm and hand. The average burned area treated was 8% (range, 2 to 20%) of the total body surface area.

Forty-one children were considered to have acquired nosocomial infections, with a mean time from admission to the first positive culture of 24 days (range, 2 to 48 days). Treatment with mupirocin was started, on average, 5 days post-MRSA isolation. Four children were readmitted with breakdown of their previously healed injuries and entered into the study.

Two patients had 11 separate sites bacteriologically and clinically assessed. Five other patients had two discrete wounds each, and 38 single wounds were treated, thereby giving a total of 59 distinct wounds treated with occlusive mupirocin dressings during the trial period. Mupirocin used in the study was supplied by Beecham Pharmaceuticals under the trade name of Bactroban.

Two topical agents were utilized on the 45 children for an average treatment period of 29 days prior to the introduction of mupirocin. Thirty-four children were treated with 10% povidone-iodine ointment every 12 h, and 11 were treated with 1% silver sulfadiazine and 0.2% chlorhexidine applied daily.

Before commencement of mupirocin therapy, swabs for culture were taken from each affected burn wound surface, from the corresponding intact skin on the side opposite to that of the burn wound, and from the anterior nares.

Each burn wound was exposed, gently wiped with dry gauze swabs to remove all visible topical ointment, and cleaned with saline washes. Daily, cotton culture swabs

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TABLE 1. Effect of mupirocin against MRSA and gram-negative bacteria in 59 discrete burn wounds

Wound organisms	No. of wounds with residual organisms (species)[a]					
	Pretreatment	During therapy at:				
		24 h	48 h	72 h	96 h	120 h
MRSA	43	8	3	0	1	0
MRSA + *Streptococcus pyogenes*	3	0	0	0	0	0
MRSA + *Streptococcus faecalis*	1	0	0	0	0	0
MRSA + *Escherichia coli*	1	0	0	0	0	0
MRSA + *Pseudomonas aeruginosa*	3	2	2 (PA)	2 (PA)	1 (PA)	0
MRSA + *Proteus mirabilis*	4	0	0	1 (PM)	1 (SA) 1 (PM/SA)	1 (PM)
MRSA + *Streptococcus faecalis* + *Pseudomonas aeruginosa*	1	1 (SA/PA)	1 (PA)	1 (PA)	1 (PA)	
MRSA + *Proteus mirabilis* + *Klebsiella pneumoniae*	3	0	1 (PM)	1 (PM)	1 (SA/PM) 1 (SA)	1 (PA) 1 (PM)

[a] SA, *S. aureus* (MRSA); PA, *Pseudomonas aeruginosa*; PM, *Proteus mirabilis*. Shills indicate presence of both types of organism in one wound.

moistened with normal saline were then rolled over the wound surface 10 times for 30 s. After samples were taken, 2% mupirocin ointment was liberally applied (±2-mm thickness) to the burned surface at 12-h intervals for 5 days. Occlusive bulk dressings were utilized. No systemic antibiotics were used during the trial period.

Organisms isolated were identified by standard methods (13). The identity of *S. aureus* was based on production of DNase or coagulase or both. Antimicrobial susceptibility patterns (including those of topical agents) were assessed by agar diffusion methods (17, 28, 35).

The wounds were inspected daily and after 5 days of treatment were assessed as bacteriologically cured when MRSA was eliminated, as improved when MRSA was replaced by a different organism, and as failed if the original MRSA was still present. Similarly, the wounds were regarded as clinically cured if no further treatment was required, as improved if the wound contained healthy-looking granulation tissue, and as failed if the wound was unchanged or had deteriorated. The clinical study period was completed only when all areas of partial- or full-thickness burn wounds had either healed spontaneously or were successfully skin grafted. Immediately following the trial period, burn swabs were taken regularly twice weekly from all unhealed wounds until skin cover was obtained. Treatment was well tolerated by all children, and no patient was withdrawn from the study.

Informed parental consent was obtained, and the study protocol was approved by the Human Ethics and Research Committee of the University of Cape Town.

RESULTS

The presence of MRSA was proved in every wound prior to the first topical application of mupirocin. Nasal carriage of MRSA was identified in 19 patients, and eight swabs from the opposite uninvolved areas yielded MRSA. There was, however, no correlation between the presence or absence of MRSA at these sites and the inability to eliminate the staphylococcus from the burn wounds.

Bacteriological elimination of MRSA was achieved within 5 days in all 59 wounds (Table 1). In 48 wounds, MRSA could no longer be cultured after 24 h of mupirocin application. The temporary reappearance of MRSA on day 4 in five discrete wounds most likely represents autocontamination, since the same organisms were found on other surface areas in these patients.

Pretreatment surface swabs revealed the cohabitation of MRSA and gram-negative bacteria in 12 of the wounds (Table 1). Two of these wounds had residual *Proteus mirabilis* and one had *Pseudomonas aeruginosa* at the end of the trial period.

Twenty of the wounds healed spontaneously after the eradication of MRSA, and in 39 the purulent granulation tissue was replaced with healthy granulation tissue, resulting in subsequent 100% graft take.

Routine posttreatment surface swabs failed to show relapse of MRSA burn wound infection after the 5-day course of therapy.

DISCUSSION

Since 1983, MRSA have become increasingly prevalent as pathogenic organisms within our burns unit, despite restrictions on antibiotic usage, improved internal environmental control, and appropriately selected topical antibacterial agents.

The infections in our patients developed usually within 3 weeks of injury. The presence of significant nasal carriage of the organisms among the patients (19 out of 45) and the high incidence of MRSA in the burns unit support the concept that contact transmission from patient to patient was the most likely source of the MRSA infection (3, 31).

Infection by MRSA leads to significant burn wound morbidity, with ongoing sepsis, graft loss, and the ever-present threat of invasive burn wound infection with an associated mortality of 20 to 40% (12, 14, 26, 30). Although commonly used antistaphylococcal antiseptics and topical agents have bactericidal activity against MRSA, a significant number of these organisms are not eliminated (16, 22, 25, 31).

Resistance to methicillin implies resistance to all β-lactam antibiotics. Although not fully understood, it appears that methicillin resistance results from the elaboration by MRSA of a novel penicillin-binding protein involved with the final stages of cell wall synthesis. This results from the transduction of an existing gene(s) which determines resistance rather than the selection of mutants among less-resistant or -susceptible strains (18). Diminished inhibition of autolytic enzymes by the antibiotic-tolerant strain (34) and, more recently, evidence of acquired resistance due to the production of increased amounts of β-lactamase by certain strains of *S. aureus* (27) are additional factors.

Mupirocin is a new nonsystemic antibiotic, exclusively developed for topical use. It has a high degree of activity against all staphylococci, including MRSA, with MICs of 0.015 to 0.06 μg/ml and an MBC of 16 μg/ml for a 99.9% kill (7). Naturally occurring relatively resistant strains requiring for inhibition an MIC of 2 μg/ml occur with a frequency of

only 10^{-9}, but it is possible to produce tolerance to 40 μg/ml with small progressive incremental concentrations of mupirocin (7). The development of resistance is probably due to the acquisition of a plasmid (32).

Topical application of mupirocin with a concentration of 20,000 μg/ml and effective penetration through 1.5-mm burn eschar would make it unlikely for these resistant strains to become a clinical problem during short-term therapy (33).

The formulation of 2% mupirocin in a polyethylene glycol base was able to eradicate MRSA rapidly from all the burn wounds and, in addition, to eliminate streptococci from three additional wounds. This confirms the findings of previous studies that mupirocin is highly active against gram-positive bacteria (37). However, part of the antibacterial effect could have been due to the antibacterial activity of the polyethylene glycol base (10). Although mupirocin failed to eradicate Pseudomonas aeruginosa and Proteus mirabilis from three wounds, the activity of mupirocin against Escherichia coli and Klebsiella pneumoniae may be of clinical significance in topical burn wound therapy. Relative insusceptibility to mupirocin is not surprising, as the MICs for enteric gram-negative bacilli range from 64 to 6,400 μg/ml (37).

Mupirocin in a polyethylene glycol ointment base (USNF) contains a mixture of polyethylene glycol 400 (58.8%) and polyethylene glycol 3350 (39.2%). Less than 0.3% of topically applied mupirocin is absorbed across intact skin, but penetration may be expected to be enhanced through burnt skin (21). It has a half-life in serum of less than 30 min and is rapidly converted to monic acid and excreted in the urine (90%). The polyethylene carrier base is similarly absorbed from the burn wound and is normally excreted by the kidney in the form of oxalic acid bound to calcium (29). In hemodynamically unstable patients and patients with poor renal function, the excretion of polyethylene glycol may be impaired, leading to reversible nephrotoxicity and specific and severe metabolic derangement (5). The average burn wound size in our study was 8% (range, 2 to 20%) of the total body surface area, and mupirocin was applied topically only to stable patients with intact renal function.

The application of mupirocin was accompanied not only by the disappearance of MRSA but also by the rapid formation of healthy granulation tissue in the nonepithelized burn wounds. In vitro studies with human fetal lung fibroblasts have shown mupirocin in low concentrations to promote cell growth, which may explain this phenomenon (6).

It can be concluded that mupirocin, with its novel mode of action, lack of cross resistance with other antibiotics, active penetration through eschar, and in vivo efficacy, may play an important role in the future treatment of MRSA burn wound infection. The cost of mupirocin in a polyethylene glycol formulation was found to be more than comparable with that of other locally obtainable antistaphylococcal topical agents.

Our final recommendations are that 2% mupirocin should be utilized as a specific therapeutic agent against MRSA and should not be used for prophylaxis. Furthermore, the safety and efficacy of mupirocin in larger burns (exceeding 20% of the total body surface area) need to be determined.

ACKNOWLEDGMENTS

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